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Biography: I have developed both animal and cell models for investigating brain function by integrating neuroscience, pharmacology, and molecular neurobiology methods, including gene induction by drug, oxidative stress, and preconditioning-induced neuroadaptation. My average citation per publication during the past two decades is greater than 50 citations per article (1991 ISI and 2001 NIH Library reports: ~6,000 citations, ~120 papers, edited 3 books). The International Biographical Centre (Cambridge, England) has awarded me as one of the International Scientist of the Year for 2003. I have also served on the Interagency Committee on Neurotoxicity, (1999-present), the Nomination Committee of American Society of Pharmacology and Experimental Therapeutics (2002 Neuropharmacology Division), Taiwanese BioScientists of America (2000 President), the Wellcome Trust (2003 reviewer), and the NIH Reactive Oxygen Species Interest Group (Coordinator 1998-present).

Research Interests: *Gene Induction in Neuroadaptation, Preconditioning-induced Hormesis, Neuroprotection, Mood, Cognition and Parkinson's Disease.* We are investigating the beneficial roles of the •NO-cGMP-PKG, Trx, CREB, Erk1/2, and c-Myc signaling pathways in gene regulation and protein expression for neuroprotection induced by CNS drugs (i.e., neurosteroid/17 β -estradiol, antidepressant/(-)-deprenyl, and cGMP modulator/YC-1). We are also exploring hormesis molecular mechanisms that can awake silent antioxidative, antiapoptotic, and neurotrophic genes for improving brain function.

Representative Recent Publications

- Rauhala, P., Lin, A. M.-Y. and Chiueh, C.C.: Neuroprotection by S-nitrosoglutathione of brain dopamine neurons from oxidative stress. *FASEB J.* 12: 165-173, 1998.
- Chiueh, C.C. and P. Rauhala: The redox pathway of S-nitrosoglutathione, glutathione and nitric oxide in cell to neuron communications. *Free Radical Res.* 31: 641-650, 1999.
- Andoh, T., Lee, S.Y. and Chiueh, C.C.: Preconditioning regulation of bcl-2 and p66^{shc} by human NOS1 enhances tolerance to oxidative stress. *FASEB J. Express*, 10.1090/fj.00-0151fje, 2000 or *FASEB J.* 14: 2144-2146, 2000.
- Andoh, T., Chock, P.B. and Chiueh, C.C.: The roles of thioredoxin in protection against oxidative stress-induced apoptosis in SH-SY5Y cells. *J. Biol. Chem.* 277: 9655-9660, 2002.
- Andoh, T., Chiueh, C.C. and Chock, P.B.: Cyclic GMP-dependent protein kinase regulates the expression of thioredoxin and thioredoxin peroxidase inducing hormesis in response to oxidative stress-induced apoptosis. *J. Biol. Chem.* 278: 885-890 2003.
- Lee, S.Y., Andoh, T., Murphy, D.L. and Chiueh, C.C.: 17 β -Estradiol activates ICI-182,780-sensitive estrogen receptors and cyclic GMP-dependent thioredoxin expression for neuroprotection. *FASEB J. Express* (in press) 2003.

Neuroprotective Strategies Against Brain Disorders Caused By Free Radicals

Principal Investigator: Chuang C. Chiueh (Ph.D.) *LCS, NIMH*

Lab staff: Gopal Krishna (Ph.D.) *LCS, NIMH*

Other NIH: P. Boon Chock (Ph.D.) *LB, NHLBI*

Extramural: Tsugunobu Andoh (Ph. D.) *Department Apply Pharmacology, Toyama Medical and Pharmaceutical University* ; Sang Y Lee (Ph. D.) *Department of Neuroscience, Pennsylvania State College of Medicine*

Duration: *from October 01, 2001 to September 30, 2002*

Total Staff Years: 1.4

Keywords: brain dopamine, gene induction, proteonomic, preconditioning, neuroprotection, nitric oxide, cGMP, PKG, MAPK/Erk1/2, c-Myc, c-Jun, CREB, thioredoxin, MnSOD, Bcl-2, MPTP/MPP⁺, oxidative stress, apoptosis, Alzheimer's dementia, Parkinson's disease

Summary:

It has been suggested that degenerative brain diseases such as Alzheimer's dementia, Parkinson's disease, stroke, head trauma, neuroAIDS, Hallervorden-Spatz syndrome, and possibly the negative subtype of schizophrenia may be due to oxidative injury caused by toxic free radicals in the brain. Our research mission is to develop neuroprotective strategies for slowing progressive neurodegeneration, to restore cognition and motor functioning, and to improve patient's quality-of-life. With recent advancements in cell and molecular biology it is now feasible to employ gene therapy as a potential treatment of brain disorders. Currently, gene therapy and multipotential stem cells have been targeted for the repair of brain injury in Parkinson's disease and Alzheimer's dementia. However, this approach requires tricky brain surgery and a dangerous intracerebral infusion procedure.

We are investigating whether gene induction evoked by drug-induced hormesis and preconditioning stress might provide an alternative procedure in gene therapy to provide neuronal adaptation or compensatory neuroprotection through the induction of

cytoprotective genes and new proteins. For this purpose, we recently developed a human brain cell model for investigating hormesis- and/or preconditioning-induced molecular mechanism including gene induction, protein expression, and associated brain functions. Preconditioning stress increases the expression of neuronal nitric oxide synthase (NOS1) leading to cGMP/PKG-dependent induction of the redox protein thioredoxin and a mitochondrial antioxidative protein MnSOD without altering the expression of heat shock proteins (e.g., HO-1 and HO-2) in human brain-derived SH-SY5Y cells. Moreover, hormesis-induced neuroprotection can be blocked by the inhibition of thioredoxin mRNA by antisense oligonucleotides and also by the inhibition of selenium containing thioredoxin reductase/peroxidase by selective enzyme inhibitors. Finally, both endogenously induced and exogenously administered thioredoxin protect human brain cells against oxidative injury caused by a parkinsonism producing neurotoxin--MPP⁺.

This cGMP/PKG mediated thioredoxin gene induction and neuroprotection may become the mechanism in common following the treatment of brain cells with analogues of estrogen and statins, all of which increase nitric oxide-mediated events through the activation of NOS expression. With the untoward complications of intracerebral injection of viral vector in gene therapy in mind, gene induction using the proposed pharmacogenetic and preconditioning procedures may be more practical than invasive gene therapy as a treatment for managing progressive neurodegeneration in brain disorders.

Publications generated by this research:

1. Andoh T, Chiueh C, Chock P (2003) Cyclic GMP-dependent protein kinase regulates the expression of thioredoxin and thioredoxin peroxidase-1 during hormesis in response to oxidative stress-induced apoptosis. *J Biol Chem* 278: 885-90. <<http://www.jbc.org/cgi/content/full/278/2/885>>
2. Andoh T, Chock PB, Chiueh CC (2002) Preconditioning-mediated neuroprotection role of nitric oxide, cGMP, and new protein expression. *Ann N Y Acad Sci* 962:1-7. [[Pubmed](#)]
3. Andoh T, Chock PB, Chiueh CC (2002) The roles of thioredoxin in protection against oxidative stress-induced apoptosis in SH-SY5Y cells. *J Biol Chem* 277:9655-60. [[Pubmed](#)]
4. Chiueh C, Andoh T (2002) Cyclic GMP-mediated preconditioning gene induction as a treatment of Alzheimer's dementia and Parkinson's disease. *In Mapping the Progress of Alzheimer's and Parkinson's Disease*. Mizuno Y, Fisher A, Hannin I,

eds. Kluwer Academic/Plenum Publishers; New York, NY/USA. 447-454 pp.

[\[Abstract\]](#)

5. Chiueh C, Hong JS, Leong SK (2002) *Nitric Oxide: Novel Actions, Deleterious Effects and Clinical Application*. Chiueh C C, Hong J S, Leong S K , eds. Annals of the New York Academy of Sciences; New York, NY/USA. Volume 962.
[\[Abstract\]](#)
6. Chiueh CC (2002) S-nitrosoglutathione (GSNO) mediates brain response to hypoxia. *Pediatr Res* 51:414. [\[Pubmed\]](#)
7. Khaldi A, Chiueh CC, Bullock MR, Woodward JJ (2002) The significance of nitric oxide production in the brain after injury. *Ann N Y Acad Sci* 962:53-9. [\[Pubmed\]](#)
8. Mohanakumar KP, Thomas B, Sharma SM, Muralikrishnan D, Chowdhury R, Chiueh CC (2002) Nitric oxide an antioxidant and neuroprotector. *Ann N Y Acad Sci* 962:389-401. [\[Pubmed\]](#)
9. Rauhala P, Andoh T, Yeh K, Chiueh CC (2002) Contradictory effects of sodium nitroprusside and S-nitroso-N-acetylpenicillamine on oxidative stress in brain dopamine neurons in vivo. *Ann N Y Acad Sci* 962:60-72. [\[Pubmed\]](#)
10. Lee, SY, Andoh, T, Murphy, DL and Chiueh, CC (2003) 17 β -Estradiol activates ICI-182,780-sensitive estrogen receptors and cyclic GMP-dependent thioredoxin expression for neuroprotection. *FASEB J. Express* (in press).
11. Chiueh, CC, Lee, SY, Andoh, T and Murphy, DL (2003) Induction of the antioxidative and antiapoptotic thioredoxin supports the neuroprotective hypothesis of estrogen. *Endocrine* (in press).

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